Amendments to the Specification

Please replace the paragraph beginning at page 5, line 12, with the following rewritten paragraph:

Various approaches have been attempted to "capture" the 2-dimensional positional relationship between molecules of a sampled array. A paraffin block has been described (~~http://cmag.cit.nih.gov/Tissuearray.htm~~ website with the host name of "cmag", domain name of "cit.nih.gov" and file extension "Tissuearray.htm") in which multiple cores (50-500) of tissue are placed in an organized grid. The device is a said to be amenable for use in a variety of experiments, including immunohistochemistry, immunofluorescence, FISH, in situ hybridization, and to provide a high throughput platform for tissue, in which hundreds of samples can be analyzed at one time, and multiple experiments can be performed on the same array (see, ~~http://www.laborel.no/Acrobat/Biogenex/Biolink%20VOL.pdf~~ the website with the host name "www", domain name of "laborel.no", and file extension "Acrobat/Biogenex/Biolink%20VOL.pdf"). Microwell and microtiter plates (e.g., Thermo Labsystems 384-Well Solid Microtiter Plate) are example of 2-dimensional arrays of partitioned grids or chambers.

Please replace the paragraph beginning at page 11, line 14, with the following rewritten paragraph:

The invention is particularly suited for use in Layered Expression Scanning (LES). LES is a new technology co-developed by the National Institutes of Health and 20/20 GeneSystems, Inc. (~~http://www.2020gene.com/~~ (Englert, C.R. *et al.* (~~2002~~2000) "LAYERED EXPRESSION SCANNING: RAPID MOLECULAR PROFILING OF TUMOR SAMPLES," Cancer Res. 60: 1526-1530). The method utilizes a layered array of membranes for molecular analysis and can be applied to a variety of life science platforms, including tissue sections, cells in culture, electrophoresis gels, multi-well plates, and tissue arrays (**Figure 1**). The technique is preferably performed by passing the sample through the series of membrane layers while maintaining two-dimensional architecture, thus permitting the concurrent measurement of different RNA transcripts or proteins in each of the individual sample elements (e.g., various cellular phenotypes in a tissue section, bands on a gel, individual wells of a microtiter plate). The method has a number of properties

that increase its utility. It is conceptually simple, requires no moving parts, can be used as an open or closed format, and maintains target biomolecules at a high concentration during the analysis process to produce sensitive measurements.

Please replace the paragraph beginning at page 32, line 26, with the following rewritten paragraph:

In addition to validating array results at the mRNA level, it is equally desirable to evaluate expression levels of the corresponding protein products. At present, the frequency with which protein expression equates with transcript levels as measured on arrays is not clear. A poll of users of tissue micro arrays produced by the National Cancer Institute (~~www.cancer.gov/tarp~~ see the website with a host name of "www", domain name "cancer.gov", and file extension "tarp") indicates that protein expression changes correlate with mRNA alterations less than 50% of the time. However, there are several caveats to consider that may be responsible for this discrepancy, including; the sensitivity and dynamic range of the methodology employed, the specificity of the antibody probe, the absolute difference in protein levels as compared to mRNA levels, and the abundance level of the protein being analyzed. Moreover, as indicated above, investigators often bias their selection of mRNAs for follow-up analysis towards those that show the largest fold-change. This may not necessarily translate to a similar difference at the protein level, particularly since protein function in the cell is affected by several parameters besides abundance.

Please replace the paragraph beginning at page 35, line 4, with the following rewritten paragraph:

Like any experimental platform, TMAs are not without limitation. The most significant drawbacks involve sensitivity, lack of quantitation, and potential selection bias of the tissue samples. Both IHC and ISH are qualitative/semi-quantitative. With several hundred tissue specimens per TMA slide, the requirement for a pathologist or experienced investigator to view and score each sample is problematic. Robust methods to analyze TMA slides in an automated fashion are facilitated by the development of a TMA database exchange (~~http://wv.lw.pathinfo.com/iib/tmafaqvl.htm~~ website with host name of "wv", domain name of "lw.pathinfo.com", and file extension "iib/tmafaqvl.htm"). Selection bias is also a potential

problem for TMAs due to the small size of the tissue core that is removed from the donor specimen. In some instances, the issue is of little concern as the expression levels of certain mRNAs and proteins are relatively uniform throughout the tissue. However, tissues are complex, multicellular entities that can contain significant intra-specimen molecular heterogeneity, particularly with respect to evolving disease processes. Therefore, a single small punch of tissue may not necessarily be representative of the overall state of the organ. Moreover, many small, but critically important structures (normal and disease-associated), are often sectioned through within the first few slides generated from a TMA block, and are thus unavailable for further study. Layered Expression Scanning, as described above, overcomes many problems related to sample bias.

Please replace the paragraph beginning at page 37, line 23, with the following rewritten paragraph:

Amplification of mRNA Samples One of the goals of the NCI's Cancer Genome Anatomy Project (CGAP) is to assess the feasibility of producing a complex transcriptome from small numbers of microdissected cells (~~http://cgap.nci.nih.gov/~~ website with host name of "cgap" and domain name of "nci.nih.gov").~~12,47.Afurtheraimwas~~ A further aim was to evaluate the effects of PCR amplification on the mRNA population. Overall, it was observed that PCR induced a bias in transcript levels to a varying degree, depending on the amplification scheme, cycle number, and primer set. However, it was also found that "intentionally biasing" the transcriptome with PCR was useful for discovering novel expression differences between cell populations. The newly discovered genes were typically expressed at low abundance levels and were not identified in experiments using non-biased cDNA. Thus, as a general strategy, it may be necessary to include a selective amplification step in some array experiments such that low-abundance transcripts can be studied. However, if this strategy is utilized, investigators must then be aware that subsequent validation experiments will be more challenging, and may also require PCR-based approaches. In other words, the identified transcripts of interest may be difficult to measure using northern blots or other techniques that do not incorporate an amplification step. Moreover, evaluation of the corresponding protein products may be particularly demanding if they are similarly expressed at low levels in the biological samples under study.